Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. THOMAS J. DRY, Rochester, *Editor*

DR. HOWARD B. BURCHELL, Rochester, *Associate Editor*

VOL. XVII JANUARY, 1948 No. 1

PENICILLIN IN THE TREATMENT OF CARDIOVASCULAR SYPHILIS

The use of penicillin in syphilis is not yet standardized, and the antispirochetal nature of the antibiotic is not yet completely understood. It follows that the planning of adequate therapy with penicillin of a late manifestation of the disease, such as cardiovascular syphilis, must depend at this time largely on recent experience with penicillin in more easily appraised types of late syphilis, as well as on past experience with arsenicals and heavy metals in the treatment of cardiovascular syphilis. Intelligent collection of further usable information presupposes a thorough knowledge of these data, of the use and action of penicillin, and of the course of the disease to be treated.

Penicillin. To insure potency it is best to use solutions made fresh daily and prepared by a sterile technic because solutions of penicillin are not self-sterilizing. Of the penicillins available, the crystalline G displays the most antispirochetal activity.[2,3] However, some experimental evidence indicates that partially purified penicillin may be even more active.[1]

Penicillin is inactivated by contact with heavy metals[4] and should not be administered in solutions containing either bismuth or arsenic.

Inherent penicillin fastness of Treponema pallidum has been observed in only one case, that of a patient with a gumma of the penis.[2] How important this will be in the treatment of cardiovascular syphilis remains to be determined.

Therapeutic efficacy depends not only on the concentration of penicillin in the tissues but also on the duration of such concentrations. Clinically these requirements can be met best by frequent intramuscular injections of an aqueous solution of the drug over a period of time. The recommended dosage at present is in the range of 5,000,000 to 10,000,000 units given in a period of fifteen to twenty-one days and nights. At the Bellevue Hospital Rapid Treatment Center 40,000 units every three hours for 150 doses (nineteen days) or 30,000 units every two hours for 200 doses (seventeen days) are the usual schedules.

Attempts have been made to maintain high concentrations of the antibiotic in the tissues both by delaying absorption from the site of injection and by delaying excretion by the renal tubules. The former has been accomplished most successfully by the use of penicillin in a peanut oil and beeswax mixture,[6] and it appears that successful ambulatory treatment of the disease can be accomplished by this method. The latter is at present most easily accomplished by a limitation of the intake of fluid and of salt during penicillin therapy.[5] "Blockade" of the tubules has been attempted by the simultaneous use of other drugs such as diodrast,[7] benzoic acid,[8] p-aminohippuric acid,[9] and caronamide.[10] It is possible that one of these methods eventually will be practical enough to eliminate the necessity for frequent intramuscular injections.

Of the reactions to penicillin in cases of early syphilis the Jarisch-Herxheimer is by far the commonest. Presumably this may occur in cardiovascular syphilis and for this reason treatment with three doses of bismuth subsalicylate of 0.2 gm. each is given intramuscularly at intervals of five days before penicillin is begun. Initial small doses of penicillin may also be given although a definition of "small" remains to be made. Although iodides have not been used preliminary to penicillin there would seem to be no contraindication to them.

Cardiovascular syphilis. Before treatment is begun, it is imperative to demonstrate not only that syphilitic disease of the heart exists, but also to learn its exact nature. For clinical purposes, cardiovascular syphilis may be divided into syphilis of the aorta (uncomplicated aortitis, aneurysm, aortic insufficiency, coronary ostial stenosis) and syphilis of the myocardium (gumma). To make the diagnosis of luetic aortitis[11] there should be a characteristic structural lesion of the aorta with a history of syphilitic infection, or a positive result of a serologic test for syphilis, or evidence of syphilitic disease elsewhere in the body. A diagnosis of uncomplicated aortitis cannot be made with any degree of certainty if in addition to the dilated aorta the possibility that some condition other than syphilis, such as arteriosclerosis, hypertension, rheumatic heart disease, rheumatic fever or hyperthyroidism is the cause. Although a dilated aorta from other causes is more frequent after the age of forty years, it is in this age group that uncomplicated aortitis of syphilitic origin is encountered most often. The diagnosis of aortic insufficiency or of aneurysm is usually easy enough to make, but coronary ostial stenosis frequently can be only suspected. If characteristic anginal pain is accompanied by an abnormal electrocardiogram, the diagnosis is fairly obvious. However, stenosis of a coronary artery sometimes causes heart failure without pain. Further, when there is aortic insufficiency of advanced degree the dynamics of the coronary circulation may be altered sufficiently to cause the

The Inter-American Society of Cardiology has authorized the meeting of the Third Inter-American Cardiological Congress, to be held in Chicago, Illinois, at the Michael Reese Hospital, from June 13 to June 17, 1948. This meeting will take place immediately before the American Heart Association annual meeting, June 18 and 19, and the American Medical Association meeting the week of June 20. Inquiries regarding the Congress may be addressed to the Offices of the Third Inter-American Cardiological Congress, at the Michael Reese Hospital, Chicago, Illinois.

46103

anginal syndrome even though ostial stenosis does not exist. These facts and also the knowledge that syphilitic heart disease may occur in association with other types must be kept in mind when the effects of penicillin on the course of cardiovascular syphilis are evaluated.

Past experience in the therapy of cardiovascular syphilis. That the incidence of cardiovascular syphilis can be greatly decreased by adequate treatment with heavy metals and arsenicals has been demonstrated.[12] It also seems certain that asymptomatic lesions of the aorta may be favorably influenced by chemotherapy. On the other hand, once symptoms of myocardial or coronary insufficiency have developed, the benefits of antisyphilitic therapy are doubtful. It is true that in a rare case of coronary ostial stenosis miraculous relief of angina may result. More often, however, there is no perceptible effect. When aortic insufficiency has progressed to the point of heart failure, or when an aneurysm has so enlarged as to cause pressure on surrounding structures, the results of treatment are usually disappointing, and occasionally the patient may be made worse (therapeutic paradox). It is not likely that penicillin differs from previously used drugs in this regard, but this remains to be proved.

Experience with penicillin in cardiovascular syphilis. Forty-nine patients with cardiovascular syphilis have been treated at the Bellevue Rapid Treatment Center under the direction of Dr. Evan W. Thomas. In eleven cases cardiovascular syphilis existed alone; in the others it was complicated by active neurosyphilis. Seventeen patients had uncomplicated aortitis; seven had diffuse dilatation or saccular aneurysms of the aorta; and twenty-five had aortic insufficiency. Of the last group, five had, in addition, diffuse dilatation of the aorta; one had an aneurysm involving the aortic arch and the innominate artery; and four were suspected of having coronary ostial stenosis. Also among those with aortic insufficiency there were seventeen who had symptoms of diminished cardiac reserve, and of these, eight had just recovered from or previously had at least one bout of congestive heart failure.

One patient received penicillin in peanut oil and beeswax; the others received aqueous solutions in dosages ranging from 3,000,000 to 6,000,000 units (one patient was given only 2,000,000 units) in twelve to nineteen days. Thirty-three had had other antisyphilitic treatment in the past. Only five (all with aortic insufficiency) received bismuth preliminary to treatment with penicillin. There were eleven patients (seven with aortitis, two with aneurysm and two with aortic insufficiency) who had received no antisyphilitic treatment of any kind previous to treatment with penicillin.

Follow-up data from a few months to three years have disclosed nothing unusual except for two patients who were admitted to the hospital in congestive heart failure. These two were treated first for myocardial insufficiency, after which penicillin was given. During the latter therapy one patient had recurrent attacks of precordial pain, such as he had had for the previous year, and died in congestive failure two months after treatment with penicillin was started. The other patient had two attacks of paroxysmal dyspnea during therapy and died five weeks later in congestive heart failure and uremia. None of the other forty-seven patients had any reaction that could be classified as a Jarisch-Herxheimer or a therapeutic paradox.

This, in general, seems to have been the experience of other observers. Of five patients[13,14,15,16] reported as experiencing precordial pain of anginal type during treatment, two had previously diminished cardiac reserve and one of these had rheumatic heart disease;[2] three had been having angina before treatment, but for two of these treatment was continued without deleterious effects. Another two patients[14] in heart failure were thought to have been made worse by penicillin. One patient[2] treated simultaneously with penicillin and tertian malaria died in heart failure four days after beginning this combined therapy. At necropsy the aorta displayed plaques of aortitis with large hemorrhages in each. One patient with complete heart block and Adams-Stokes seizures was treated with penicillin with little effect.[17] Syncopal seizures have continued to occur.

Cardiovascular complications of syphilis treated with penicillin. Unusual rhythms or electrocardiographic abnormalities during treatment of any kind of syphilis with penicillin have not been reported. In the Bellevue series one patient was observed to have recurrent attacks of auricular fibrillation during secondary syphilis which promptly terminated soon after treatment with penicillin was begun. The phenomenon simply suggests that further observations should be made along this line.

Summary. Insufficient data are available to make any statement regarding the effectiveness of penicillin in cardiovascular syphilis. Reactions to treatment are rare. Those reported have been in cases of the anginal syndrome or heart failure, and were as readily attributed to the natural course of the disease as to the penicillin.

Charles E. Kossmann, M.D.
Gerald Flaum, M.D.
New York, N. Y.

REFERENCES

1. Dunham, W. B., and Rake, Geoffrey: The relative activity of partially purified penicillin and of crystalline penicillin G on treponema pallidum. Am. J. Syphilis, Gonorrhea, and Venereal Diseases. 29:214-228, 1945.
2. Moore, J. E.: Penicillin in Syphilis. Charles C. Thomas, Springfield, 1946.
3. Eagle, Harry: The relative activity of penicillins F, G, K and X against spirochetes and Streptococci in Vitro. J. Bact. 52:81-88, 1946.
4. Abraham, E. P., and Chain, E.: Purification and some physical and chemical properties of penicillin. Brit. J. Exp. Path. 23:103-115, 1942.
5. Finland, M.: Use of penicillin in infections other than bacterial endocarditis. Advances in Internal Medicine. Vol. 2: 350-415. Interscience Publishers, 1947, New York.
6. Romansky, M. J., and Rittman, G. E.: Penicillin. 1. Prolonged action in beeswax-peanut oil mixture. 2. Single injection treatment of gonorrhea. Bull. U. S. Army Med. Dept. No. 81:43-49, 1944.
7. Rammelkamp, C. H., and Bradley, S. E.: Excretion of penicillin in man. Proc. Soc. Exper. Bio. & Med. 53:30, 1943.
8. Bronfenbrenner, Jack, and Favour, C. B.: Increasing and prolonging blood penicillin concentrations following intramuscular injections. Science 101:673-674, 1945.
9. Beyer, K. H., Flippin, Harrison, Verwey, W. F., and Woodward, Roland: The effect of para-aminohippuric acid on plasma concentration of penicillin in man. J. A. M. A. 126:1007-1009, 1944.
10. Boger, W. P., Kay, C. F., Eisman, S. H. and Yeoman, E. E.: High penicillin plasma concentration by the use of caronamide, a compound that inhibits penicillin excretion by the renal tubules. Presented at 39th Annual Meeting, American Society for Clinical Investigation, May 4, 1947.
11. Nomenclature and Criteria for Diagnosis of Diseases of the Heart. American Heart Association. 230-236, 1945.
12. Maynard, E. P., Jr., and Lingg, Claire: The prevention of cardiovascular syphilis. Brooklyn Hospital Journal. 4:18-25, 1946.
13. Dolkart, R. E., and Schwemlein, G. X.: The treatment of cardiovascular syphilis with penicillin. J. A. M. A. 129:515-516, 1945.
14. Porter, R. R.: Penicillin in cardiovascular syphilis. Read by title at the Scientific Session. American Heart Association, June 6-7, 1947.
15. Tucker, H. A., and Farmer, T. W.: Penicillin in cardiovascular syphilis; early reactions to administration. Presented at a symposium of the Syphilis Study Section, National Institute of Health, Washington, D. C. April 17, 1947.
16. Russek, H. J., Cutler, J. C., Fromer, S. A., and Zohrman, B. L.: Treatment of cardiovascular syphilis with penicillin. Annals Int. Med. 25:957, (Dec.), 1946.
17. Levine, S. A.: Personal communication.

NOTES

NOTES